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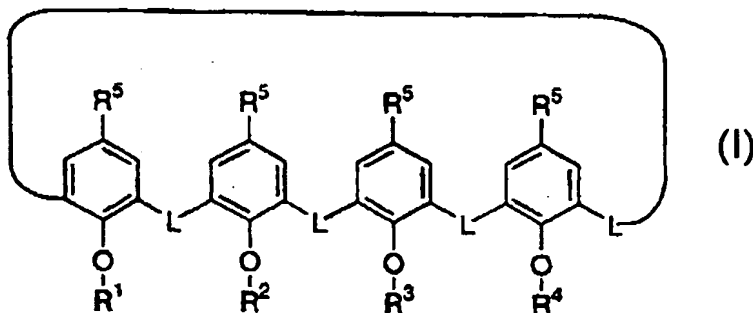
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Calixarenes

(57) Disclosed are "acid-thioamide" calixarenes of formula (I), wherein: L is [-CR<sub>2</sub>-] or [-O-CH<sub>2</sub>-O-] and is the same or different between each aryl group; R<sup>5</sup> is H, NO<sub>2</sub>, halogen, or C<sub>1</sub>-C<sub>10</sub> aliphatic hydrocarbyl group, C<sub>6</sub>-C<sub>20</sub> aryl group, C<sub>6</sub>-C<sub>20</sub> hydrocarbylaryl group, any of which is optionally substituted by one or more halo or oxo groups or interrupted by one or more oxo groups, and R<sup>5</sup> is the same or different on each aryl group; R<sup>1</sup> comprises a carboxy group which is or is not protonated or protected; two groups out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H; and the one group out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> not being H comprises a thioamide group. Dimer calixarenes are also disclosed. Also disclosed are methods of use of such calixarenes for the purposes of metal sequestration, especially of lanthanides and actinides. Also disclosed are processes for preparing the calixarenes. Further disclosed are sensors and sensor components utilising the calixarenes of the present invention.



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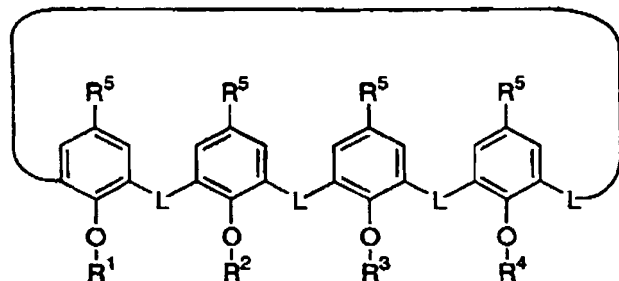
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(54) Title: CALIXARENES



(I)

(57) Abstract: Disclosed are "acid-thioamide" cal-  
ixarenes of formula (I), wherein: L is [-CH<sub>2</sub>-] or [-O-  
CH<sub>2</sub>-O-] and is the same or different between each  
aryl group; R<sup>5</sup> is H, NO<sub>2</sub>, halogen, or C<sub>1</sub>-C<sub>10</sub>aliphatic  
hydrocarbyl group, C<sub>6</sub>-C<sub>20</sub> aryl group, C<sub>6</sub>-C<sub>20</sub> hydro-  
carbylaryl group, any of which is optionally substi-  
tuted by one or more halo or oxo groups or inter-  
rupted by one or more oxo groups, and R<sup>5</sup> is the same  
or different on each aryl group; R<sup>1</sup> comprises a car-  
boxy group which is or is not protonated or protected;  
two groups out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H; and the one  
group out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> not being H comprises  
a thioamide group. Dimer calixarenes are also dis-

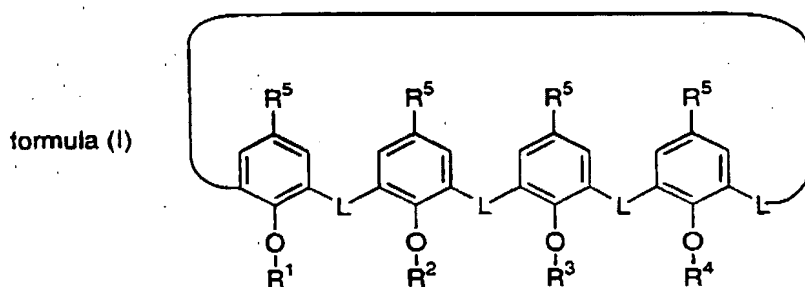
closed. Also disclosed are methods of use of such calixarenes for the purposes of metal sequestration, especially of lanthanides and  
actinides. Also disclosed are processes for preparing the calixarenes. Further disclosed are sensors and sensor components utilising  
the calixarenes of the present invention.

## Calixarenes

This invention relates to novel calixarenes, methods of their preparation and uses thereof, in particular for the sequestration of metals.

Calixarenes have been suggested as being useful for the sequestration of certain ionic metallic species. European Patent Publication No. 0 432 989 and WO 97/17322 describe a number of calixarene and oxacalixarene derivatives having metal sequestering properties and review some of the prior art in this field. It is the object of the present invention to provide calixarenes with an improved ability to sequester metals.

In accordance with the present invention, calixarenes of a formula (I)



10 wherein:

L is [ - CH<sub>2</sub> - ] or [ -O-CH<sub>2</sub>-O- ] and is the same or different between each aryl group;

R<sup>5</sup> is H, -NO<sub>2</sub>, halogen, or C<sub>1</sub> - C<sub>10</sub> aliphatic hydrocarbyl group, C<sub>6</sub> - C<sub>20</sub> aryl group, C<sub>6</sub> - C<sub>20</sub> hydrocarbylaryl group, any of which is optionally substituted by one or more halo or oxo groups or interrupted by one or more oxo groups, and R<sup>5</sup> is the same or different on each aryl group;

R<sup>1</sup> comprises a carboxy group which is or is not protonated or protected;

two groups out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H; and

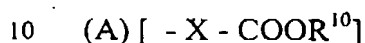
the one group out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> not being H comprises a thioamide group.

The combination of acid/ester and thioamide groups is not found in the prior art and leads to improved metal sequestration properties.

Most preferably,  $R^2$  and  $R^4$  are H and  $R^3$  comprises a thioamide group.

L is preferably  $[-CH_2-]$  between each of the aryl groups and  $R^5$  may be a tertiary butyl.

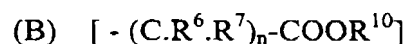
In a preferred embodiment, the carboxy group  $R^1$  conforms to the general formula (A):



wherein X is a  $C_1$ , a  $C_2$  or a  $C_3$  carbon chain which is a part of an aliphatic hydrocarbyl group, aryl group or hydrocarbylaryl group, any of which is optionally substituted by one or more halo, oxo or nitro groups; and  $R^{10}$  is H or a protecting group being a salt or an ester group.

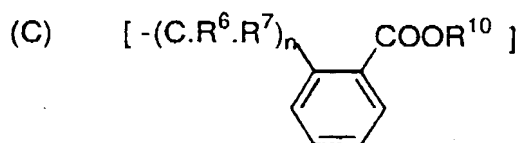
15 Furthermore, in a preferred embodiment  $R^{10}$  is H and the aliphatic hydrocarbyl group, aryl group or hydrocarbylaryl group of formula (A) is substituted by one or more groups which cause a reduction in the pKa of the carboxylic acid group with respect to an unsubstituted molecule.

20 Most preferably,  $R^1$  is of the general formula (B):



25 wherein n is 1, 2 or 3 and  $R^6$  and  $R^7$  are H or halogen and is the same or different on each carbon.

Alternatively,  $R^1$  is of the general formula (C):

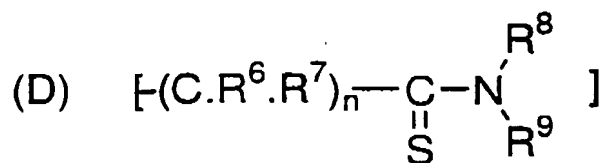


wherein  $n$  is 0 or 1 and  $R^6$  and  $R^7$  are H or halogen and is the same or different on each carbon and wherein the phenyl ring of the benzoic acid group is optionally substituted by one or more halo, oxo or nitro groups. In this embodiment,  $R^{10}$  may be H and the phenyl ring of the benzoic acid of formula (C) may be substituted by one or more groups which cause a reduction in the  $pK_a$  of the carboxy group with respect to an unsubstituted molecule.

In structures (B) and (C) above,  $n$  is preferably 1 and  $R^6$  and  $R^7$  are preferably both H.

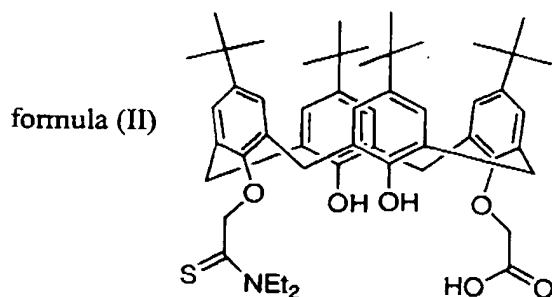
10 In unprotected acid embodiments, the aliphatic hydrocarbyl group, aryl group or hydrocarbylaryl group of X in formula (A) is preferably substituted by one or more groups causing a reduction in the  $pK_a$  of the carboxy group with respect to the unsubstituted molecule.

15 It is preferred that the thioamide group  $R^2$ ,  $R^3$  or  $R^4$  of formula (I) is of the general formula (D):



20 wherein  $n$  is 1, 2 or 3 and  $R^6$  and  $R^7$  are H, halogen, or  $C_1$ - $C_{10}$  aliphatic hydrocarbyl group, and is the same or different on each carbon, and wherein  $R^8$  and  $R^9$ , which is the same or different, are H or  $C_1$  -  $C_{10}$  aliphatic hydrocarbyl group which is optionally substituted by one or more halo groups, or is optionally interrupted by a keto group or is optionally a cycloaliphatic ring formed by  $R^8$  and  $R^9$  together, or is optionally conjugated to a second calixarene.

In a further preferred embodiment the calixarene is of formula (II)



It is optional that where calixarenes are of the formulae (I) or (II) then some or all of phenyl groups of the calixarene ring are further peripherally substituted, in such a way that the sequestering abilities of the calixarene are not compromised.

In a further embodiment of the invention, a dimer can be made wherein one of the  $R^8$  and  $R^9$  groups is conjugated to a second calixarene.

The  $R^8$  or  $R^9$  group of one calixarene can be conjugated to the  $R^8$  or  $R^9$  group of the other calixarene, optionally through a spacer group  $R^{11}$ , the optional spacer group  $R^{11}$  being  $C_1$ - $C_6$  aliphatic hydrocarbyl group,  $C_6$ - $C_{10}$  aryl group,  $C_6$ - $C_{16}$  hydrocarbylaryl group, any of which may optionally be substituted by one or more halo or oxo groups or interrupted by one or more oxo groups.

In a second aspect of the invention, there is provided a method of sequestering metals comprising contacting the metals with a calixarene in accordance with the present invention.

Preferably, the method is carried out at a pH of between 2 and 11. It is most preferable that the pH at which the method is carried is buffered. The buffer used may be citrate. A low pH will decrease the likelihood of metal precipitation, whereas a high pH will increase the dissociation of unprotected acid groups.

The method may comprise the following steps:

(i) dissolving the calixarene in an hydrophobic organic solvent;

(ii) mixing the organic solvent with an aqueous phase containing metal ions;

(iii) agitating the organic solvent and aqueous phase together;

(iv) recovering the metal from the organic phase.

This method enables the recovery of the extracted metal from the organic phase by contacting with a relatively small volume of acid.

The method may conveniently be used to sequester a metal chosen from a Lanthanide, U, Hg, Am, Pb, Sr, Bi, Cd, Ag and Y. The calixarene should be present in excess.

In the method, the calixarene may optionally be solid phase bound e.g. in a polymer support.

This should be readily achieved by the person skilled in the art, given the disclosures concerning the use of polymer supports in US 4 642 362, 4 699 966 and 4 447 585 and in European Patent publication no. 0 217 656.

In a third aspect of the invention, the calixarenes can be incorporated into an ion-selective polymeric membrane for an electrochemical sensor comprising a supporting matrix.

In a fourth aspect of the invention, a process for preparing the calixarenes in accordance with the present invention comprises the sequential steps of:

(i) bis-esterification of a calix[4]arene;

(ii) deprotection of a first ester group to form a first acid group;

(iii) chlorination of the first acid group to form an acyl chloride;

(iv) substitution of the chlorine group in the said acyl chloride with a diamine moiety to form an amide group; and

(v) substitution of the oxygen group in the amide group with a sulphur group to form a thioamide moiety.

- 5 This produces ester-thioamides in good yield and is a relatively simple process.

The process may further comprise a subsequent step of deprotecting the second ester group to form a second acid group. This produces an acid-thioamide in good yield and is relatively simple.

- 10 The invention will now be described by way of example only with reference to the following drawings of which:

Figure 1 is a schematic showing a synthetic route for the ester-thioamide A960 and acid-thioamide A961, both compounds being in accordance with the present invention; and

- 15 Figure 2 shows the variation in % extraction of Cadmium ( $\text{Cd}^{2+}$ ) ions with the molar ratio of Calixarene: $\text{Cd}^{2+}$  for prior art compound acid-amide A954 (patent application number WO 97/17322, Fig. 15), and two materials in accordance with the present invention (ester-thioamide A960 and acid-thioamide A961) at pH=9.4.

*Example 1 - synthesis of the ester-thioamide A960*

- 20 A960 was synthesised using the route shown in Figure 1. The precursor A953 was prepared in accordance with patent publication number WO 97/17322. Lawesson's reagent (0.49 g, 1.2 mmol) was added to a solution of ester-amide A953 (1.0g, 1.17 mmol) in toluene (20  $\text{cm}^3$ ) and the mixture was heated at 80 °C for 4 hr. After cooling to room temperature, the toluene was removed under reduced pressure to give a yellow oil. This oil was dissolved in  
25 acetonitrile (15  $\text{cm}^3$ ) and filtered through an alumina pad. Dropwise addition of water to the filtrate afforded a yellow precipitate, which was removed by filtration and recrystallised from dichloromethane-ethanol to afford A960 as yellow prismatic crystals (0.95g, 94%). The structure of this compound was confirmed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry and X-ray crystallography.



*Example 2 - synthesis of the acid-thioamide A961*

A961 was synthesised using the route shown in Figure 1. The ester-thioamide A960 was synthesised by the route shown in Figure 1 and Example 1. Potassium hydroxide (0.036g, 0.65 mmol) was added to a solution of ester-thioamide A960 (0.5g, 0.58 mmol) in ethanol (25 cm<sup>3</sup>) and the solution heated under reflux for 2 hr. The ethanol was reduced in volume to approximately 5 cm<sup>3</sup> and 1M HCl added to precipitate A961 as a pale yellow powder which was recrystallised from dichloromethane-hexane (0.41g, 85%). The structure of this compound was confirmed by NMR and mass spectrometry.

The synthesis of other related compounds in accordance with the present invention can be readily undertaken by one skilled in the art using the teaching of the present invention in association with the teaching of patent publication number WO97/17322.

*Example 3 - ability of the compounds in accordance with the present invention to sequester metals*

Figure 2 shows the ability of the calixarenes in accordance with the present invention A960 and A961 to extract cadmium ions at pH 9.4. Data are also presented for a prior art material, A954 (prepared in accordance with patent application, publication number WO97/17322, example 11 and figure 15 therein). Equal volumes of aqueous cadmium cyanide solution (pH 9.4, [Cd<sup>2+</sup>]=0.238mMolar) and a solution of a calixarene in dichloromethane were mixed for 15 minutes by stirring. The aqueous and organic phases were then allowed to separate for about 30 minutes. The aqueous layer (Aq1) was then removed, and the organic layer was washed with a nitric acid blank (pH 9.4). The aqueous and organic layers were allowed to separate for about 30 minutes, and the aqueous layer was then removed (Aq2). Aq1 contained the cadmium ions that had not been extracted by the calixarenes, whereas Aq2 contained the cadmium ions that had been extracted by the calixarenes (and subsequently liberated by acidification of the organic layer). Aq1 and Aq2 were made up to known volumes. ICP AES (inductively coupled plasma atomic emission spectroscopy) was then used to determine the concentration of cadmium ions in the solutions. These figures can readily be used to determine the percentage extraction of cadmium for a given ratio of concentration of calixarene:cadmium.

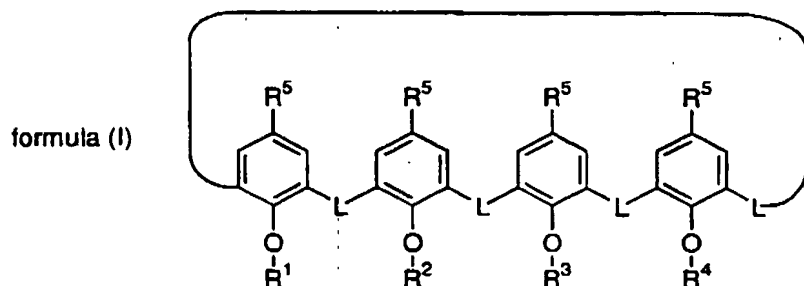
Figure 2 indicates that both the acid-thioamide A961 and the ester-thioamide A960 are capable of extracting cadmium ions from solution. The order of efficiency of extraction is acid-thioamide, A961 > acid-amide, A954 > ester-thioamide, A960. The order can be explained by the fact that both A961 and A954 have a proton that can be readily lost from the acid substituent. The resulting anion will attract and retain cadmium ions more effectively than the (usually uncharged) ester group. The acid-thioamide (A961) forms complexes with cadmium more readily than the acid-amide (A954) because the S atom in A961 is a "softer" atom than the O atom in A954, and is thus more polarisable and thus is more likely to form a complex with a  $\text{Cd}^{2+}$  ion, which is itself a "soft" ion.

Hence, the compounds in accordance with the present invention may be used in applications in which the sequestration of metal ions is important, such as liquid waste decontamination and water purification.

Furthermore, the compounds in accordance with the present invention may be used in sensors, wherein the compounds form part of an ion-selective polymeric membrane for an electrochemical sensor. The ionophore is dispersed within a supporting matrix. The matrix is polymeric and also typically comprises an ion exchange material such as potassium tetra parachlorophenyl borate. The supporting membrane may further comprise a plasticiser such as 2-nitrophenyl octyl ether, dioctylphthalate, dibutylsebacate and dioctylphenylphosphonate. The membrane will be attached to an electrode and the presence of selective ions will cause a change in the electrical characteristics of the electrode (relative to a reference electrode, such as a Calomel electrode) and thus be registered by the sensor.

## CLAIMS

## 1. Calixarenes of a formula (I)



5 wherein:

L is [ - CH<sub>2</sub> - ] or [ - O-CH<sub>2</sub>-O- ] and is the same or different between each aryl group;

10 R<sup>5</sup> is H, NO<sub>2</sub>, halogen, or C<sub>1</sub> - C<sub>10</sub> aliphatic hydrocarbyl group, C<sub>6</sub> - C<sub>20</sub> aryl group, C<sub>6</sub> - C<sub>20</sub> hydrocarbylaryl group, any of which is optionally substituted by one or more halo or oxo groups or interrupted by one or more oxo groups, and R<sup>5</sup> is the same or different on each aryl group;

R<sup>1</sup> comprises a carboxy group which is or is not protonated or protected;

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two groups out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are H; and

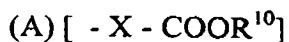
the one group out of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> not being H comprises a thioamide group.

20 2. Calixarenes as claimed in claim 1 wherein R<sup>2</sup> and R<sup>4</sup> are H and R<sup>3</sup> comprises a thioamide group.

3. Calixarenes as claimed in claim 1 or claim 2 wherein L is [ - CH<sub>2</sub> - ] between each of the aryl groups.

25

4. Calixarenes as claimed in any one of claims 1 to 3 wherein  $R^5$  is a tertiary butyl.
5. Calixarenes as claimed in any one of claims 1 to 4 wherein the carboxy group  $R^1$  conforms to the general formula (A):



wherein X is a  $C_1$ , a  $C_2$  or a  $C_3$  carbon chain which is a part of an aliphatic hydrocarbyl group, aryl group or hydrocarbylaryl group, any of which is optionally substituted by one or more halo, oxo or nitro groups; and  $R^{10}$  is H or a protecting group being a salt or an ester group.

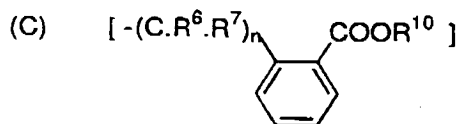
6. Calixarenes as claimed in claim 5 wherein  $R^{10}$  is H and the aliphatic hydrocarbyl group, aryl group or hydrocarbylaryl group of formula (A) are substituted by one or more groups which cause a reduction in the pKa of the carboxylic acid group with respect to an unsubstituted molecule.

7. Calixarenes as claimed in claim 5 wherein  $R^1$  is of the general formula (B):



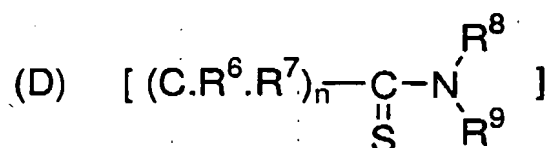
wherein n is 1, 2 or 3 and  $R^6$  and  $R^7$  are H or halogen and is the same or different on each carbon.

8. Calixarenes as claimed in claim 5 wherein  $R^1$  is of the general formula (C):



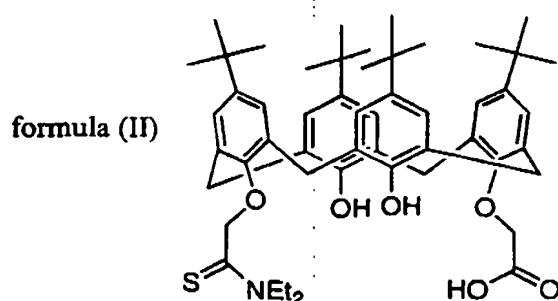
wherein n is 0 or 1 and  $R^6$  and  $R^7$  are H or halogen and is the same or different on each carbon and wherein the phenyl ring of the benzoic acid group is optionally substituted by one or more halo, oxo or nitro groups.

9. Calixarenes as claimed in claim 8 wherein  $R^{10}$  is H and the phenyl ring of the benzoic acid of formula (C) is substituted by one or more groups which cause a reduction in the pKa of the carboxy group with respect to an unsubstituted molecule.
10. Calixarenes as claimed in any one of claims 5 to 9 wherein n is 1 and  $R^6$  and  $R^7$  are both H.
11. Calixarenes as claimed in any one of the preceding claims wherein the thioamide group  $R^2$ ,  $R^3$  or  $R^4$  of formula (I) is of the general formula (D):



- wherein n is 1, 2 or 3 and  $R^6$  and  $R^7$  are H, halogen, or  $C_1$ - $C_{10}$  aliphatic hydrocarbyl group, and is the same or different on each carbon, and wherein  $R^8$  and  $R^9$ , which is the same or different, are H or  $C_1$  -  $C_{10}$  aliphatic hydrocarbyl group which is optionally substituted by one or more halo groups, or is optionally interrupted by a keto group or is optionally a cycloaliphatic ring formed by  $R^8$  and  $R^9$  together, or is optionally conjugated to a second calixarene.

12. A calixarene of formula (II)



13. Calixarenes of the formulae (I) or (II) as claimed in claim 1 or 12 wherein some or all of phenyl groups of the calixarene ring are further peripherally substituted.

14. A calixarene dimer comprising a calixarene as claimed in either claim 11 wherein one of the R<sup>8</sup> and R<sup>9</sup> groups is conjugated to a second calixarene.

15. A dimer as claimed in claim 14 wherein the R<sup>8</sup> or R<sup>9</sup> group of one calixarene is conjugated to the R<sup>8</sup> or R<sup>9</sup> group of the other calixarene, optionally through a spacer group R<sup>11</sup>, the optional spacer group R<sup>11</sup> being C<sub>1</sub>-C<sub>6</sub> aliphatic hydrocarbyl group, C<sub>6</sub>-C<sub>10</sub> aryl group, C<sub>6</sub>-C<sub>16</sub> hydrocarbylaryl group, any of which may optionally be substituted by one or more halo or oxo groups or interrupted by one or more oxo groups.

16. A method of sequestering metals comprising contacting the metals with a calixarene as claimed in any one of the preceding claims.

17. The method as claimed in claim 16 wherein the method is carried out at a pH of between 2 and 11.

18. The method as claimed in claim 16 or 17 wherein the pH at which the method is carried is buffered.

19. The method as claimed in claim 18 wherein the buffer used is citrate.

20. The method as claimed in any one of claims 16 to 19 comprising the following steps:

(i) dissolving the calixarene in an hydrophobic organic solvent;

(ii) mixing the organic solvent with an aqueous phase containing metal ions;

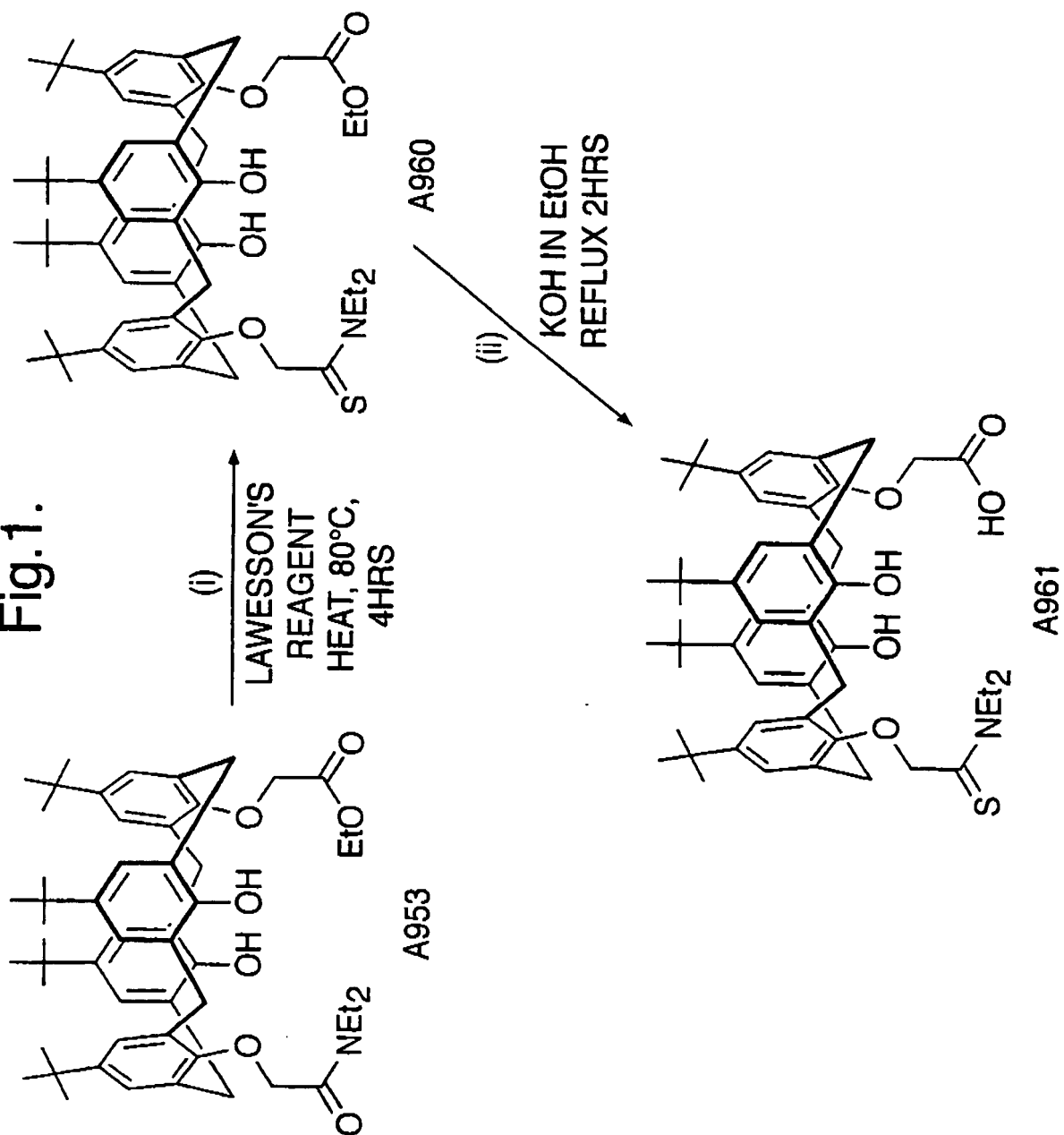
(iii) agitating the organic solvent and aqueous phase together;

(iv) recovering the metal from the organic phase.

21. The method as claimed in any one of claims 16 to 20 wherein the metal is selected from a Lanthanide, U, Hg, Am, Pb, Sr, Bi, Cd, Ag and Y.
22. The method as claimed in any one of claims 16 to 21 further characterised in that the  
5 calixarene is solid phase bound.
23. An ion-selective polymeric membrane for an electrochemical sensor comprising a supporting polymer matrix and a calixarene as claimed in any one of claims 1 to 15.
- 10 24. A process for preparing a calixarene as claimed in any one of claims 1 to 15 comprising the sequential steps of:
- (i) bis-esterification of a calix[4]arene;
  - 15 (ii) deprotection of a first ester group to form a first acid group;
  - (iii) chlorination of the first acid group to form an acyl chloride;
  - (iv) substitution of the chlorine group in the said acyl chloride with a diamine moiety to form  
20 an amide group; and
  - (v) substitution of the oxygen group in the amide group with a sulphur group to form a thioamide moiety.
- 25 25. A process as claimed in claim 24, wherein the process comprises a subsequent step of deprotecting the second ester group to form a second acid group.

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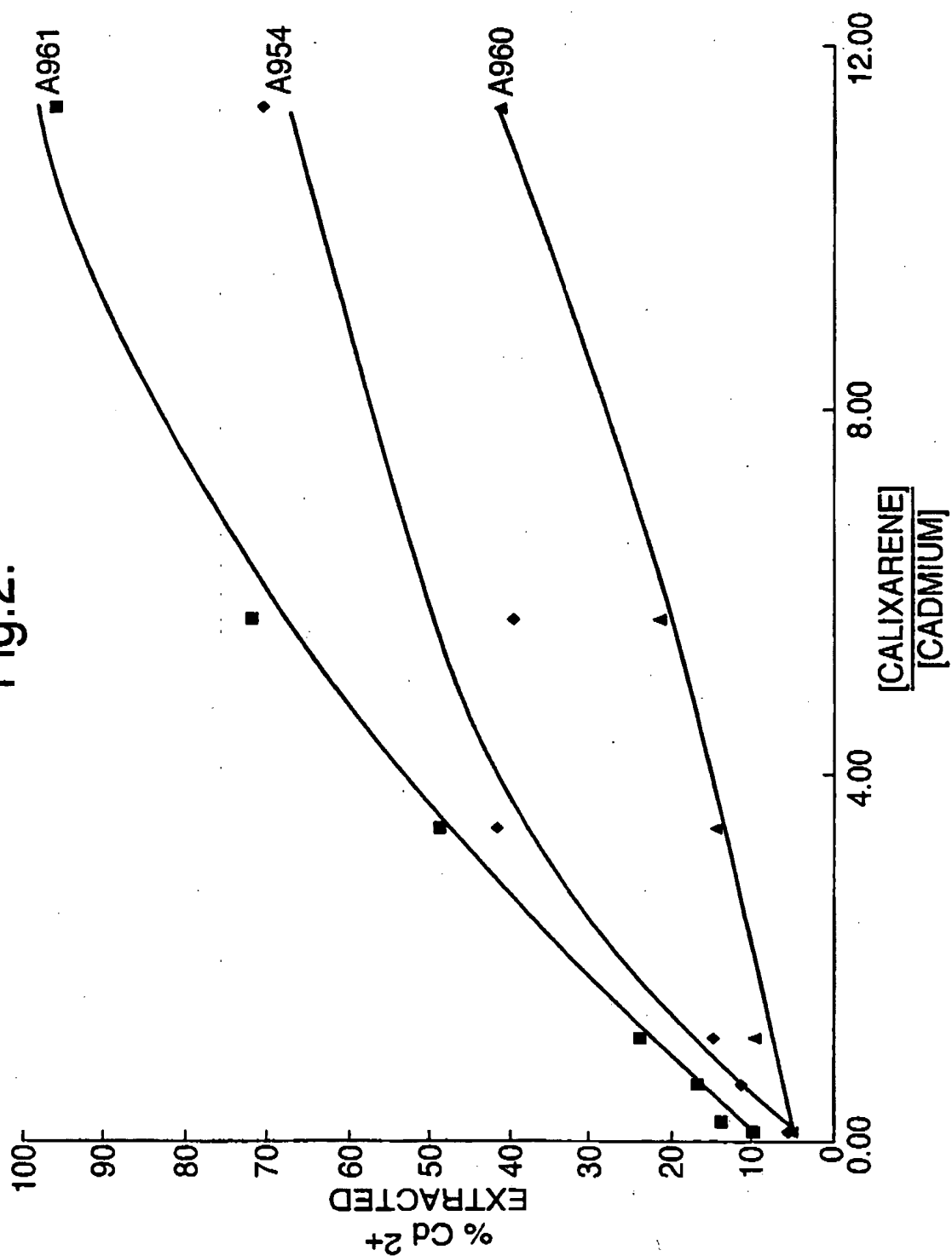
Fig.1.





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Fig.2.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04729

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C327/42 C22B3/34 G01N27/333

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C22B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17322 A (THE SECRETARY OF STATE FOR DEFENCE ) 15 May 1997 (1997-05-15) cited in the application examples; claims	1-22,24, 25
A	EP 0 432 989 A (LOCTITE (IRELAND) LTD) 19 June 1991 (1991-06-19) cited in the application example 1	1,16
A	P.L.H.M. COBBEN ET AL: J. AM. CHEM. SOC., vol. 114, no. 26, 1992, pages 10573-10582, XP002162182 page 10574, chart I	1,23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/04729

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